Learning from reward and prediction

Geugies, Hanneke

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Decreased reward circuit connectivity during reward anticipation in major depression

Chapter 02

Abstract

An important symptom of major depressive disorder (MDD) is the inability to experience pleasure, possibly due to a dysfunction of the reward system. Despite promising insights regarding impaired reward-related processing in MDD, circuit-level abnormalities remain largely unexplored. Furthermore, whereas studies contrasting experimental conditions from incentive tasks have revealed important information about reward processing, temporal difference modeling of reward-related prediction error (PE) signals might give a more accurate representation of the reward system. We used a monetary incentive delay task during functional MRI scanning to explore PE-related striatal and ventral tegmental area (VTA) activation in response to anticipation and delivery of monetary rewards in 24 individuals with major depressive disorder versus 24 healthy controls. Furthermore, we investigated group differences in temporal difference related connectivity with a generalized psychophysiological interaction (gPPI) analysis with the VTA, ventral striatum (VS) and dorsal striatum (DS) as seeds during reward versus neutral, both in anticipation and delivery. Relative to HCs, MDD patients displayed decreased temporal difference-related activation in the VS during reward anticipation and delivery combined. Moreover, gPPI analyses revealed that during reward anticipation, MDD patients exhibited decreased functional connectivity between the VS and ACC/mPFC, anterior insula, superior/middle frontal gyrus (SFG/MFG), thalamus, and precuneus compared to HC. Moreover, MDD patients showed decreased functional connectivity between the VTA and bilateral insula compared to HC during reward anticipation. Exploratory analysis separating medication free patients from patients using antidepressant revealed that these decreased functional connectivity patterns were mainly apparent in the MDD group that used antidepressants. These results suggest that MDD is characterized by alterations in reward circuit connectivity rather than isolated activation impairments. These findings represent an important extension of the existing literature as improved understanding of neural pathways underlying depression-related reward dysfunctions, may help currently unmet diagnostic and therapeutic efforts.

Introduction

One of the core characteristics of major depressive disorder (MDD) is anhedonia, the inability to experience pleasure. Anhedonia affects approximately 37% of individuals diagnosed with MDD (Pelizza and Ferrari, 2009). A dysfunction of the reward system is thought to comprise the neural basis of anhedonia (Der-Avakian and Markou, 2012; Pizzagalli, 2014; Treadway and Zald, 2011; Whitton et al., 2015). The presence of anhedonia has been found to predict poor treatment response in MDD patients (Spijker et al., 2001; Uher et al., 2012), and impairments in reward-relates processes appear to be insufficiently addressed by current treatments (Calabrese et al., 2014).

In recent years, a significant number of studies have sought to identify the neural correlates of reward-related processes (Berridge et al., 2009; Der-Avakian and Markou, 2012; Pujara and Koenigs, 2014; Whitton et al., 2015). Most notably, the dorsal striatum ([DS], i.e. the caudate), the ventral striatum ([VS], nucleus accumbens) and ventral tegmental area (VTA) have been found to play an important role in reward processes (Fareri et al., 2008; O'Doherty, 2004; Russo and Nestler, 2013). More specifically, depressed individuals showed decreased striatal activity (ventral and dorsal) in response to reward anticipation (Pizzagalli et al., 2009; Smoski et al., 2009; Zhang et al., 2013) and reward delivery (Admon, Nickerson et al., 2015; Smoski et al., 2009; Zhang et al., 2013). Furthermore, increased activation was observed in frontal regions including the middle frontal gyrus and the anterior cingulate cortex (ACC) in MDD patients during reward anticipation (Zhang et al., 2013).

Neural reward processing has been related to phasic firing of dopaminergic neurons (Schultz, 1998; Tobler et al., 2005). In incentive trials, dopamine activity is dependent on the combination of reward anticipation (expectancy) and the subsequent delivery (i.e. consumption or outcome) of the reward. When a reward is anticipated but omitted, there is a decrease in dopaminergic firing (referred to as a negative prediction error [PE]) whereas a phasic burst of dopamine (i.e. positive PE) is observed when the reward delivery is better than expected (Schultz, 1998). Positive and negative PEs can be used as parametric modulators in order to reflect the magnitude of dopaminergic activation. PEs have been predominantly used in fMRI related reinforcement learning models in order to capture reward learning signals (Dombrovski et al., 2015; Geugies et al., 2019; Gradin et al., 2011; Kumar et al., 2008; Rothkirch et al., 2017). However, PEs also exist in incentive fMRI tasks without an explicit learning compound like (card-) guessing tasks or the monetary incentive delay (MID) task (Chase et al., 2013; Staudinger et al., 2009; Ubl, Kuehner, Kirsch, Ruttorf, Diener et al., 2015; Yacubian et al., 2006), although PEs here are often not distinctively examined.

Whereas studies contrasting experimental conditions from incentive tasks have revealed important information about the neural correlates of reward processing, temporal difference modeling of reward-related PE-signals might give a more accurate representation of the reward system (Staudinger et al., 2009). So far, only few studies investigated reward-related PE signaling in depression. Reinforcement learning studies found increased activation of the VTA (Geugies et al., 2019; Kumar et al., 2008) and decreased VS (Gradin et al., 2011; Kumar et al., 2008) and DS (Gradin et al., 2011) activity in (remitted) MDD. Reward expectancy studies revealed reduced frontal and striatal activity during anticipation of gain (Chase et al., 2013;

Ubl, Kuehner, Kirsch, Ruttorf, Diener et al., 2015) and losses (Ubl, Kuehner, Kirsch, Ruttorf, Diener et al., 2015) in MDD. Moreover, these altered reward-related processes in depressed individuals seem to be substantially associated with anhedonia. Several studies report a negative correlation between anhedonia and basic reward activity in the VS (Der-Avakian and Markou, 2012), as well as temporal difference-related VS activity (Rothkirch et al., 2017), during reward processing in MDD. However, one other recent study found that higher anhedonia was associated with higher VS activity during anticipation in MDD (Ubl, Kuehner, Kirsch, Ruttorf, Diener et al., 2015).

Despite these promising insights regarding neural correlates, there is evidence that MDD is associated with alterations in connectivity between components of the reward circuitry in addition to dysfunction of individual brain areas (Admon, Nickerson et al., 2015). Admon and colleagues (2015) found decreased connectivity between the caudate (i.e. DS) and the dorsal ACC in response to monetary loss outcome and increased connectivity between these two regions in response to monetary gain outcome in MDD patients (Admon, Nickerson et al., 2015). In line with this finding, Dombrovski et al. (2015) demonstrated disrupted connectivity between the DS and prefrontal cortex during probabilistic reversal learning in patients with late-life depression (Dombrovski et al., 2015). Despite these interesting findings, it remains largely unexplored if alterations in connectivity between other elements of the reward circuitry, besides the DS, exist and whether these alterations can be linked to depression.

Therefore, this study aims to investigate PE-related striatal and VTA activation in MDD in response to anticipation and delivery of monetary rewards, and explore the association with anhedonia. Furthermore, we also want to investigate, with an exploratory approach, whether MDD is characterized by alterations in connectivity within the reward circuitry, by looking at abnormal striatal (VS and DS) and VTA connectivity in response to rewards. In line with literature, we expected reduced PE-related activity in MDD patients compared to healthy controls (HC) in the VS (Kumar et al., 2008; Pizzagalli et al., 2009) and DS (Admon, Nickerson et al., 2015; Pizzagalli et al., 2009) and increased activation of the VTA (Kumar et al., 2008) during both reward anticipation and outcome. In addition, we expected a negative correlation between reward activity and anhedonia severity during reward processing (Der-Avakian and Markou, 2012; Rothkirch et al., 2017). Moreover, decreased reward-circuitry connectivity in MDD patients compared to HC was expected (Admon, Nickerson et al., 2015).

Material and Methods

Participants

Data was derived from the Depression In the Picture (DIP) neuroimaging study conducted at the University Medical Center Groningen investigating the neural correlates of depression. Permission for the study was obtained from the local ethics committee and written informed consent obtained from all participants. Twenty-four MDD patients were recruited through specialized mental health care institutions and advertisements at the participating institutions and satisfied the following criteria: (1) presence of at least mild depressive symptoms defined as a Beck Depression Inventory (BDI-II) (Beck et al., 1996) score >13 at screening, (2) current depressive disorder diagnosis according to the MINI-SCAN (Nienhuis et al., 2010),

administered by trained postgraduate students, and 3) age ≥ 18 years. Twenty-four age- and sex-matched HC were recruited by means of advertisements at public places and in local newspapers. Inclusion criterion for HC was a BDI-II< 9 and HCs were excluded if there was a personal history of psychiatric disorders. General exclusion criteria for both groups were: (1) a current or lifetime diagnosis of drug dependence, excluding nicotine dependence or history of alcohol dependence/abuse, (2) current neurological problems that may interfere with task performance, (3) inadequate comprehension of the Dutch language, (4) MRI contraindications such as metal implants, (5) presence of any cardiovascular disease. Exclusion criteria specific for MDD patients were: (1) presence of current or lifetime psychiatric disorders other than MDD or anxiety disorders, (2) concrete suicidal plans, (3) psychotropic medication use other than SSRI/SNRI/TCA or infrequent benzodiazepine use.

Task

After a short practice run before scanning, participants performed a monetary incentive delay (MID) task to assess reward processing. The task was a shortened version of the task design previously described by Pizzagalli and colleagues (2009). The task consisted of 4 blocks of 13 trials with a total of 20 reward trials, 20 neutral trials, and 12 loss trials. Each trial consisted of the presentation of a cue (+€ / ±€ / -€ indicating a reward, neutral or loss trial), a target presentation (blue square), and reward feedback (i.e. +€1.85). Cues and feedback were presented for 1.5s and the target was presented for 0.5s. The inter-stimulus interval varied between trials (inter-stimulus interval between cue and target: 3.5s – 9.5s; inter-stimulus interval between target and feedback: 2.5s – 8.5s) to prevent expectancy effects, as was the duration of the fixation cross presented between trials (3s – 7s). Stimuli were presented in E-prime 2 (Psychology Software Tools, Pittsburgh, PA). Given our aims, neural correlates of loss trials were not examined, but maintained for comparability with previous MID studies and to prevent participants from associating neutral trials with a loss experience. Participants were instructed to press the button on an MRI-compatible button box as quickly as possible after target presentation on each trial, in order to maximize their chances of obtaining a reward. If a participant neglected to press the button, no reward could be obtained for that trial. Reward success rates were fixed at 80% to ensure a total obtained reward of €10 per participant. This reward was added to the financial compensation for participation, to increase motivation of the participants.

Data acquisition

Functional images were acquired on a Philips 3-Tesla MR-scanner equipped with a 32-channel SENSE head coil. T2*-weighted images were acquired with the following parameters: 425 whole-brain volumes; repetition time 2000 ms; echo time 20 ms; flip angle 70°; 37 axial slices; no slice gap; 64x61 matrix; voxel size 3.5 x 3.5 x 3.5 mm; field of view (FOV) 224 x 129.5 x 224 mm. High resolution T1-weighted anatomical images were acquired with the following parameters: repetition time 9 ms; echo time 3.6 ms; 170 sagittal slices; 256 x 231 matrix; voxel size 1 x 1 x 1 mm.

Temporal difference learning model

In order to parametrically modulate fMRI signals, PEs after (repeated) rewards and during (unexpected) non-rewards were computed for the time series of stimuli. Unexpected non-rewards occurred when the button was pressed on time but no reward was obtained. The calculation of temporal difference PEs was derived from Staudinger et al. (2009). This model defines a reward expectation EV as:

$$EV = m \times p$$

Where *m* is the expected gain and *p* is the gain probability. As expected gain we chose average win and loss values from the practice run. The gain probability was set to 0.8 as 80% of the reward trials resulted in an actual win and the other 20% in an omission.
The PE was defined as:

$$PE = R - EV$$

Where *R* is the amount of reward that was actually received.

Analysis

Sample characteristics

Sample characteristics and behavioral data were analyzed in SPSS package v22.0 (SPSS Inc., USA). We used independent samples t-tests, $\chi 2$-tests and non-parametric Mann-Whitney U-test to compare demographic and clinical variables between MDD patients and the HC group.

Behavioral data

We used repeated measures analysis of variance to examine main effects of group (MDD and control) and condition (reward and neutral) and a group x condition interaction with reaction times as dependent variable.

Imaging data

Pre-processing and analysis was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab R2013a (The MathWorks Inc., Natick, MA). First the PAR/REC files were converted to NIfTI format. Both structural and functional images were reoriented in AC-PC alignment. Functional images were realigned. To detect possible motion artefacts, frame wise displacement (FD) was calculated. Motion was deemed excessive when FD > 0.9 for a certain volume (Siegel et al., 2014). The amount of volumes with excessive motion was minimal (< 10%) for all participants, which we regarded acceptable. Functional images were co-registered to the structural T1 images. All images were spatially normalized to Montreal Neurological Institute (MNI) space. Finally, all images were smoothed using an 8 mm Full Width Half Maximum Gaussian kernel.

Temporal difference-related activity

For each participant, first-level hemodynamic responses for the different conditions were modelled with a general linear model. Reward anticipation, reward delivery, neutral anticipation, neutral delivery, loss anticipation and loss delivery were defined as regressors. E-prime log files were used to extract onset times and durations. Prediction errors were entered into the model as parametric modulators. Low frequency noise was removed via a high pass filter (128s). Furthermore, realignment parameters, their first derivatives and FD calculations were added to the model to address residual movement not corrected by realignment. For all participants, first-level contrasts for the total temporal difference-related activation (RewardAnticipation + RewardDelivery > Neutral) and for reward anticipation (RewardAnticipation > NeutralAnticipation) and reward delivery (RewardDelivery > NeutralDelivery) separate were defined and taken to second level.

A *priori* regions of interest (ROI) were the striatum (caudate and nucleus accumbens) and VTA. ROI selection was based on the Reinforcement Learning Atlas (Pauli et al., 2018). At second-level, we used a one sample t-test to investigate main effects of task (RewardAnticipation + RewardDelivery > Neutral contrast). Main effect images were thresholded at $p < 0.001$ uncorrected. We used independent two-sample t-tests to determine group differences. As we had clear a priori regions of interest, a small volume correction (SVC) was applied with significance defined as $p < 0.05$ FWE corrected.

Generalized psycho-physiological interaction (gPPI) analysis

We investigated group differences in temporal difference-related connectivity during the reward task with a generalized psychophysiological interaction (gPPI) analysis with VTA, ventral striatum and dorsal striatum as seeds during reward versus neutral, both in anticipation and delivery. The seeds were extracted from the Reinforcement Learning Atlas (Pauli et al., 2018) and were resliced to match the dimensions of the functional data. On first level, separate gPPI models for each seed were estimated for each participant. Each first level model contained regressors for the task conditions, one regressor for the seed, and regressors for the seed x condition interaction. Furthermore, realignment parameters, their first derivatives and FD calculations were added to the model to address residual movement not corrected by realignment. Effects for the obtained interaction variable were convolved using a canonical hemodynamic response function (HRF). For all participants, first-level contrasts for reward anticipation (RewardAnticipation > NeutralAnticipation) and reward delivery (RewardDelivery > NeutralDelivery) separate were defined and taken to second level. On second level, we used independent two-sample t-tests to determine group differences. An initial threshold was set to $p < 0.005$ uncorrected, where group differences were defined significant at $p < 0.017$ (Bonferroni correction: $p = 0.05/3$ ROIs), FWE cluster-level corrected.

In order to interpret temporal difference-related activation and connectivity findings, we also investigated correlations with anhedonia with separate multiple regression analyses with temporal difference-related activation signal and connectivity findings respectively as the dependent variable, while anhedonia scores, group and the group x anhedonia interaction were examined. Anhedonia scores were calculated as a subscale measurement of the Beck Depression Inventory (loss of pleasure, interest, energy and libido; (Pizzagalli et al., 2009)).

gPPI exploratory analysis: effect of medication

Because of two recent meta-analyses that indicate that some types of antidepressants may have a small positive effect on cognitive functioning (Keefe et al., 2014; Rosenblat et al., 2015), we chose to do an exploratory analysis by splitting up the patient group into a medication free group (MDDmed-, n = 14) and an antidepressant using MDD group (MDDmed+, n = 10) in order to rule out any medication effects on the results.

Results

Sample characteristics

No significant differences were observed between MDD patients and HC (Table 1). The exploratory analysis with three groups (HC vs MDD with/without medication) also revealed no significant differences between groups (Table 1).

Behavioral results

We observed no significant differences in reaction times between the two groups (MDD versus HC) and observed no significant group x condition interaction (Figure 1). There was a main effect of condition ($F_{2,92}$ = 10.79, p < 0.001). Post-hoc least significant difference (LSD) comparisons revealed that all participants reacted significantly faster to reward trials than to neutral trials (p < 0.001).

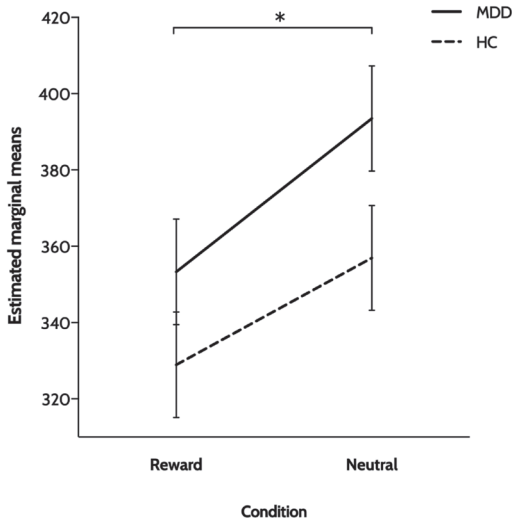

Figure 1. Reaction times for different conditions. Error bars refer to standard error of the mean.
*p < 0.001

Functional MRI results

Main effect of task

We found a main effect of task in reward related areas, especially when we incorporated the parametric modulation of the BOLD-response using the prediction errors (Figure 2).

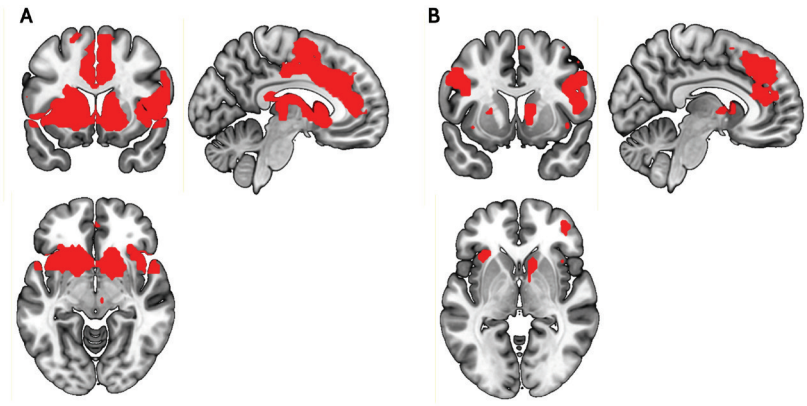

Figure 2. Main effect of task (RewardAnticipation + RewardDelivery > Neutral contrast thresholded at $p < 0.001$ uncorrected). A) Task effect with TD modulation. B) Task effect without TD modulation

Table 1. Demographic and Clinical Characteristics

				MDD		HC vs. MDD all		HC vs. MDD_{med+}, MDD_{med-}	
		Healthy controls (N = 24)	MDD (all) (N = 24)	med+ (N = 10)	med- (N = 14)	Test-statistic	*p*	Test-statistic	*p*
Age (years)	Mean (range)	44 (24-67)	44 (23-69)	45 (30-66)	44 (23-69)	$t(46) = -0.11$	0.91	$F(2,45) = 0.04$	0.97
Sex	Male/Female	7/17	6/18	5/5	1/13	$X^2(1) = 0.11$	0.75	$X^2(2) = 5.53$	0.06
Education levels[a]	N (1/2/3/4/5/6/7)	0/1/0/1/6/9/7	0/0/0/1/7/8/8	0/0/0/1/3/2/4	0/0/0/0/4/6/4	$X^2(4) = 1.20$	0.88	$X^2(8) = 3.71$	0.88
BDI-II at MRI[b]	Median (IQR)	1 (0-3)	27.5 (16-31.75)	17.5 (12.5-28)	28.5 (22-33)	$U = 0$	< 0.001	$t(22) = -1.89$	0.07[d]
Anhedonia MRI[c]	Median (IQR)	0 (0-0)	3 (2-3)	2.5 (1.75-3.25)	3 (1.75-3)	$U = 30.5$	< 0.001	$U = 67$	0.89[d]
Comorbid anxiety	N (GAD/SAD/AG)	-	4/1/1	1/1/1	3/0/0	-	-	$X^2(3)$	0.35[d]
AD use	N (SSRI/SNRI/TCA)	-	6/2/2	-	-	-	-	-	-

MDD = major depressive disorder, [a]Level of educational attainment (Verhage, 1964). Levels range from 1 to 7 (1 = primary school not finished, 7 = preuniversity/university degree), [b]Beck Depression Inventory (BDI-II) total scores, [c]Beck Depression Inventory (BDI-II) anhedonia-subscores, [d]MDDmed+ versus MDDmed-, IQR = Inter-quartile range, GAD = generalized anxiety disorder, SAD = social anxiety disorder, AG = agoraphobia, AD = antidepressant

Temporal difference-related activity results

We found a trend towards decreased temporal difference-related activation in the VS in MDD patients compared to HC during reward anticipation and delivery combined ($p_{FWE,SVC}$ = 0.052, Table 2, Figure 3).

Table 2. Between group TD-related activation ROIs

Contrast		Location	Voxels	MNI coordinates	*z*	*p**
Reward Anticipation + Reward Consumption x TD	HC > MDD	VS	18	(6, 8, -4)	2.83	0.052
		Caudate	72	(-6, 11, 8)	2.85	NS
			79	(18, 8, 11)	2.58	NS
	MDD > HC	No clusters survived threshold				

*FWE peak level corrected + small volume corrected, NS = difference not significant after small volume correction

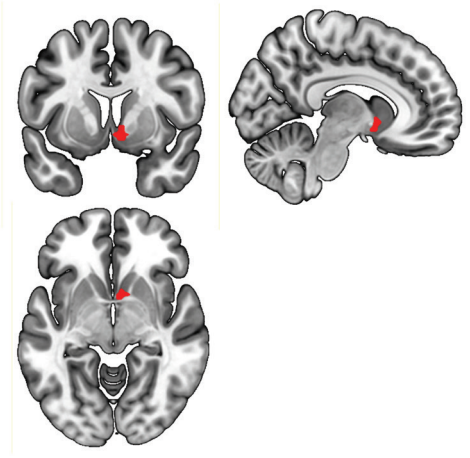

Figure 3. TD-related activity in the ventral striatum. MDD patients show decreased VS activity compared to HC during reward anticipation and consumption combined ($p_{FWE,SVC}$ = 0.052).

Functional connectivity (gPPI) results HC vs MDD

Our gPPI analyses revealed that during reward anticipation, MDD patients exhibited decreased functional connectivity between the VS and ACC/mPFC, anterior insula, superior/middle frontal gyrus (SFG/MFG), thalamus, and precuneus compared to HC (Table 3, Figure 4). Moreover, MDD patients showed decreased functional connectivity between the VTA and bilateral insula compared to HC during reward anticipation (Table 3, Figure 5). No group differences were found for the DS seed. For all seeds, no group differences were found in functional connectivity during reward delivery.

Table 3. Between group gPPI connectivity, HC vs. MDD

Seed	Contrast		Location	Voxels	MNI coordinates	*z*	*p**
VS	Reward Anticipation > Neutral	HC > MDD	ACC/mPFC	589	(-18, 59, 17)	4.36	< 0.001
			Insula Left	378	(-33, 14, 20)	4.01	< 0.001
			SFG/MFG	238	(39, 8, 50)	4.38	0.005
			Precuneus/thalamus/ visual/cerebellum	7024	(-21, -67, 38)	5.02	< 0.001
		MDD > HC	No clusters survived threshold				
VTA	Reward Anticipation > Neutral	HC > MDD	Insula Left	739	(-51, -16, 8)	4.11	< 0.001
			Insula Right	197	(36, -7, 14)	3.71	0.010
			Visual cortex	245	(-15, -67, -4)	3.77	0.003
		MDD > HC	No clusters survived threshold				
DS	Reward Anticipation > Neutral	HC > MDD	No clusters survived threshold				
		MDD > HC	No clusters survived threshold				

*FWE cluster level corrected, Bonferroni corrected

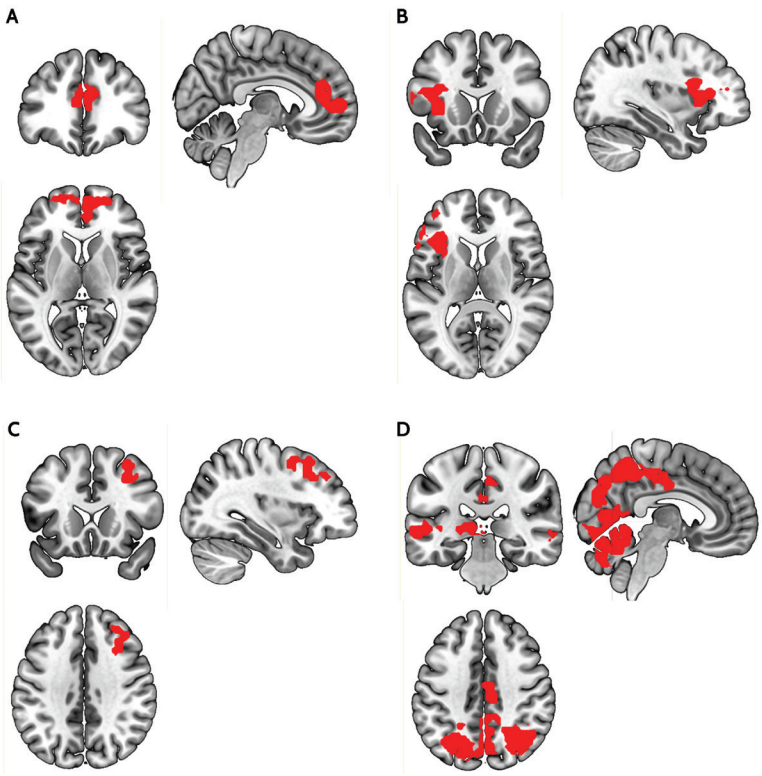

Figure 4. gPPI results VS-seed. During reward anticipation, MDD patients show decreased functional connectivity between the VS and A) ACC/mPFC ($Z = 4.36$, $p < 0.001$), B) left insula ($Z = 4.01$, $p < 0.001$), C) SFG/MFG ($Z = 4.38$, $p = 0.005$), and D) precuneus/thalamus/cerebellum ($Z = 5.02$, $p < 0.001$) compared to HC

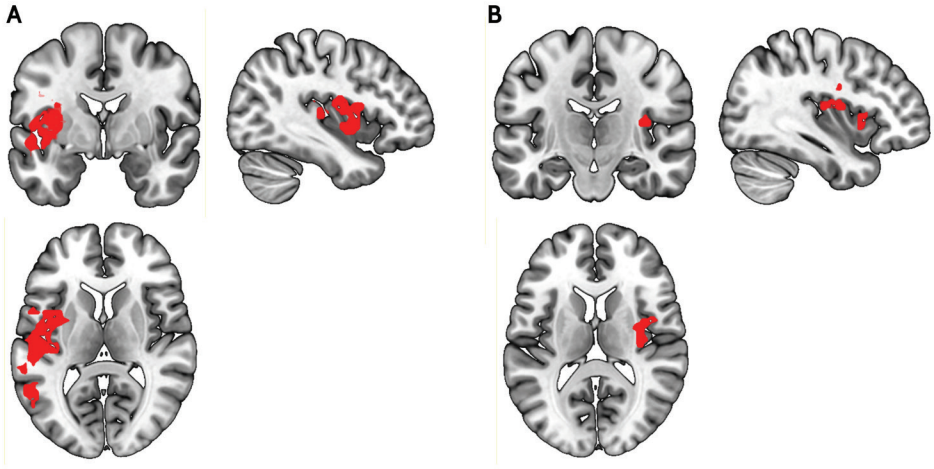

Figure 5. gPPI results VTA-seed. During reward anticipation, MDD patients showed decreased functional connectivity between the VTA and (A) the left insula (Z = 4.11, $p < 0.001$) and (B) right insula (Z = 3.71, $p = 0.01$) compared to HC

gPPI results exploratory analysis: effect of medication

When separating the medication free ($MDDmed^-$) from the antidepressant using MDD patients ($MDDmed^+$) we found that $MDDmed^+$ patients showed decreased functional connectivity between the VS and mPFC, insula, SFG/MFG, precuneus and thalamus compared to HC during reward anticipation (Table 4, Figure 6). The medication-free subjects were not significantly different from HC. Furthermore, both $MDDmed^+$ and $MDDmed^-$ patients showed decreased functional connectivity between the VTA and insula compared to HC during reward anticipation (Table 4, Figure 7). No group differences were found in functional connectivity during reward delivery.

Table 4. Exploratory analysis, between group gPPI connectivity, HC vs. $MDDmed^+$ and $MDDmed^-$

Seed	Contrast		Location	Voxels	MNI coordinates	*z*	*p**
VS	Reward Anticipation > Neutral	HC > $MDDmed^+$	mPFC	247	(18, 59, 8)	3.86	0.004
			Insula Left	300	(-48, -19, -7)	4.15	0.001
			SFG/MFG	204	(36, 8, 50)	4.00	0.010
			Thalamus	311	(-3, -13, 11)	3.62	0.001
			Precuneus/visual/ cerebellum	3975	(36, -58, 47)	5.26	< 0.001
		HC > $MDDmed^-$	No clusters survived threshold				
		$MDDmed^+$ > HC	No clusters survived threshold				
		$MDDmed^-$ > HC	No clusters survived threshold				
VTA		HC > $MDDmed^+$	Insula Left	360	(-51, 2, -1)	4.49	< 0.001
			Insula Right	182	(63, -28, 2)	3.86	0.015
		HC > $MDDmed^-$	Insula Left	300	(-51, -16, 8)	3.66	0.001
		$MDDmed^+$ > HC	No clusters survived threshold				
		$MDDmed^-$ > HC	No clusters survived threshold				

*FWE cluster level corrected, Bonferroni corrected

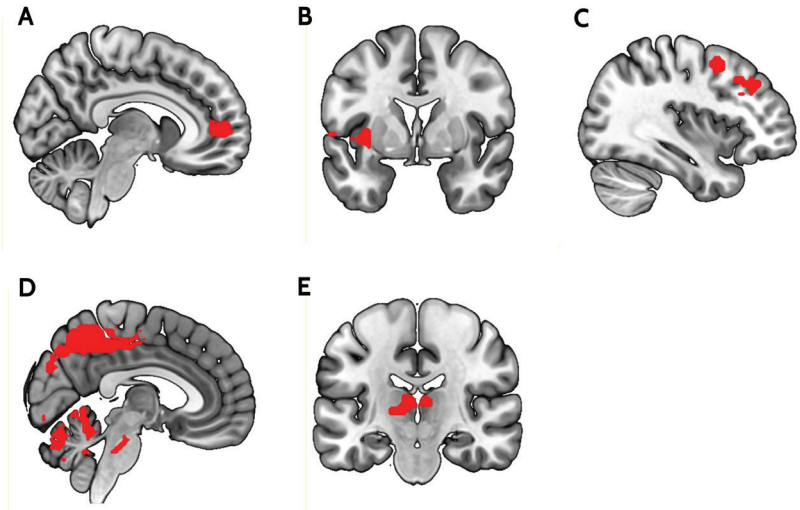

Figure 6. gPPI results exploratory analysis VS seed. During reward anticipation, MDDmed^{+} patients showed decreased functional connectivity between the VS and (A) mPFC (Z = 3.86, p = 0.004), (B) left insula (Z = 4.15, p = 0.001), (C) SFG/MFG (Z = 4.00, p = 0.01), (D) precuneus/cerebellum (Z = 5.26, p < 0.001), and (E) thalamus (Z = 3.62, p = 0.001) compared to HC

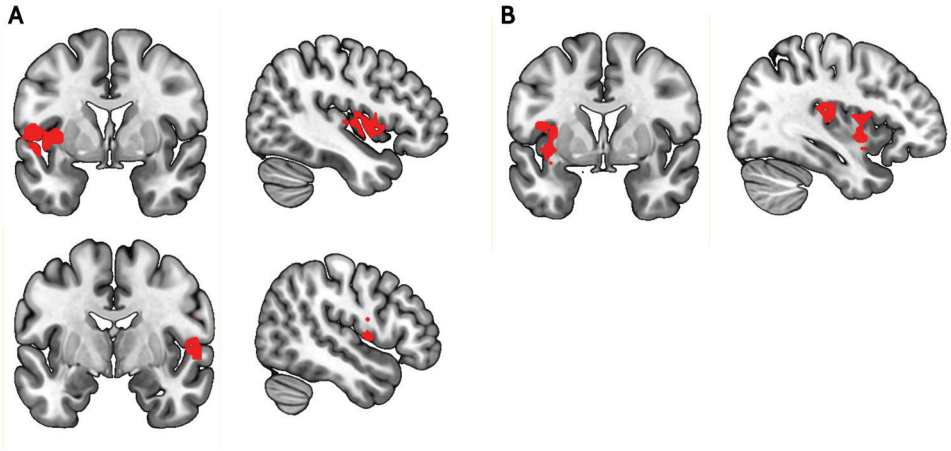

Figure 7. gPPI results exploratory analysis VTA-seed. During reward anticipation, (A) MDDmed^{+} patients showed decreased functional connectivity between the VTA and left insula (Z = 4.49, p < 0.001) and right insula (Z = 3.86, p = 0.015) and (B) MDDmed^{-} patients showed decreased functional connectivity between the VTA and the left insula (Z = 3.66, p = 0.001) compared to HC

Correlation with anhedonia

We found no correlation between temporal difference-related reward activation/connectivity and anhedonia scores.

Discussion

The present study explored temporal difference-related response of the reward system during a monetary incentive delay task. We demonstrated that parametric modulation of the BOLD-response with prediction errors optimizes monetary incentive task activation. Using the temporal difference, we found decreased temporal difference-related activation in the VS in MDD patients compared to HC during reward anticipation and delivery combined. We found no group differences in temporal difference-related VTA activation. Secondly, we exploratorily investigated connectivity between reward circuitry brain areas with gPPI. We revealed that during reward anticipation, MDD patients exhibited an overall decrease in reward circuit connectivity compared to HC. Exploratory analysis separating medication free patients from patients using antidepressant revealed that these decreased functional connectivity patterns were mainly apparent in the MDD group that used antidepressants. Of note, all group differences were not related to the reward delivery condition, suggesting that these results are specific to reward anticipation.

The decrease in temporal difference-related activation in the VS, is supported by a robust body of evidence showing decreased VS activation in MDD during basic reward processing (Pizzagalli et al., 2009; Ubl, Kuehner, Kirsch, Ruttorf, Diener et al., 2015). Although our results have to be interpreted with caution, as this effect narrowly missed statistical significance (p = 0.052 FWE/SVC-corrected), this finding is bolstered by the fact that it also replicates previous results specifically investigating temporal difference-related VS activation (Kumar et al., 2008). No differences in reaction times were observed between groups, indicating that fMRI findings were not confounded by differences between groups in task performance. A similar lack of group differences on behavioral responses has been reported before (Knutson et al., 2008; Pizzagalli et al., 2009; Ubl, Kuehner, Kirsch, Ruttorf, Diener et al., 2015).

Impaired reward functioning is further corroborated by our gPPI findings of decreased functional connectivity between the reward system and several other brain areas including the insula and thalamus. The thalamus is important in detecting sensory information and relay this information through projections to the VS and insula (Cho et al., 2013). The insula has been linked to anticipating future rewards (Tanaka et al., 2004) and delayed gratification (Wittmann et al., 2007). Moreover, a recent meta-analysis of 42 studies has demonstrated functional connectivity between the VS and the thalamus and insula (Cauda et al., 2011). This connectivity is critical in detecting salient external stimuli and adjust behavior to these incentives (Cho et al., 2013). Our observation of decreased VS-insula connectivity during anticipation of rewards in MDD suggests that MDD patients have difficulties in integrating salient information into motivational processes to shape behavior. Besides this involvement, insula activity also appears during PE encoding of reward (Haruno and Kawato, 2006; Jones et al., 2011), suggesting encoding of a salience PE (Gu et al., 2016; Metereau and Dreher, 2013). The decreased VTA-insula functional connectivity in MDD suggests an impairment in encoding these salience PEs.

We also found decreased functional connectivity between the VS and the ACC/mPFC and superior/middle frontal gyrus during reward anticipation in MDD patients. Animal studies provide fundamental evidence that the mPFC is part of the reward system and is involved

in reward seeking and reward effort (Tzschentke, 2000). The mPFC receives dopaminergic projections from the VTA and sends glutamatergic projections back to the VTA and VS. These functional interactions have been suggested to strongly modulate the mesocorticolimbic dopamine circuit (Tzschentke and Schmidt, 2000) and have been suggested to be specifically related to reward anticipation (Balleine et al., 2007; Knutson, Fong et al., 2001; Wittmann et al., 2007). Animal studies report that inactivation of the mPFC reduces the firing rate of VS neurons in response to reward-predictive cues (Ishikawa et al., 2008). Disrupted functional connectivity from the VS to the mPFC during anticipation could hamper activation of the mPFC, which in turn may alter the feedback projections to the VTA and VS, resulting in mesolimbic reward circuitry abnormalities. These current results substantiate the notion that dysfunctions in fronto-striatal activity during reward anticipation are an important marker of MDD (Zhang et al., 2013).

Besides their role in the reward circuitry, the ACC/mPFC are, together with the precuneus, important areas of the default mode network (DMN). In healthy controls, functional connectivity has been reported between the VS and DMN regions including the precuneus and mPFC (Di Martino et al., 2008) during rest. A previous study in depressed individuals found that compared with controls, depressed subjects showed decreased connectivity between the precuneus/PCC and the striatum (Bluhm et al., 2009), which is in line with the current results. The DMN has been found to support internal mental activity and is also critical for self-relevance and self-referential processing (Raichle, 2015). It is possible that decreased VS-DMN connectivity causes an impairment in assigning salience to external and internal stimuli, potentially leading to aberrant salience.

When separating the medication free patients from the patients using antidepressants, we found that the decreased connectivity patterns were mainly apparent in the MDD group that used antidepressants. Given the association between antidepressant use and diminished neural responses of the reward system (McCabe et al., 2010), and the suggestion that SSRI treatment blunts dopaminergic activity, explaining symptoms such as anhedonia and affective blunting (Goodwin et al., 2017), it can be argued that reward related connectivity may be affected by antidepressant treatment, however, this remains purely speculative.

No differences between groups were observed in temporal difference-related activity during reward delivery. This finding is in line with studies by Stoy et al. (2012) and Ubl et al. (2015) who also report depression related dysfunctions during reward anticipation but not during the receipt of reward. Given that other studies report decreased fronto-cingulate-striatal activation during the reward delivery phase (Forbes et al., 2009; Knutson et al., 2008; Pizzagalli et al., 2009), and considering the modest sample size of our study, our null findings should be interpreted with caution. Future studies should reveal the extent of dysfunctions during reward delivery in MDD.

The present study did not identify a correlation between brain activation/connectivity of the reward system and hedonic capacity. This lack of an association is in contrast to other papers (Chase et al., 2010; Ubl, Kuehner, Kirsch, Ruttorf, Diener et al., 2015). However, differences in task paradigms and anhedonia questionnaires might account for these differences. E.g., Chase et al. (2010) used a probabilistic selection task and Ubl et al. (2015) employed a modified version of the MID task we used. In both studies hedonic capacity was measured with the

Snaith Hamilton Pleasure Scale (SHAPS), while we assessed anhedonia with the BDI anhedonia subscore, which resulted in a narrow range of anhedonia scores. The SHAPS embodies a more extensive measurement of consummatory anhedonia which may have been more sensitive in mapping anhedonia levels.

Strengths and limitations

The current design enabled us to explore functional connectivity alterations in the reward circuitry, which is a novel feature compared to measuring altered activity of reward related brain areas during reward processing, as supported by previous work (Admon, Holsen et al., 2015; Pizzagalli et al., 2009; Smoski et al., 2009; Zhang et al., 2013). Furthermore, this study is novel in modeling temporal difference signals in a MID task which might give a more accurate representation of reward-related brain activity and connectivity. Nevertheless, potential limitations exist. First, no temporal difference-related VTA task activity was found. The nature of the task used in this study may account for the absence of temporal difference-related activity in the VTA. Traditionally, the MID task has been designed to investigate changes in neural activity in response to basic processing of reward. Activation in the VTA, elicited from firing of dopaminergic neurons during reward-related learning, is most likely best reflected by a classical conditioning paradigm, for example used by Kumar et al. (2008). Second, ten out of twenty-four MDD patients were receiving antidepressants at time of scanning. Splitting up the patient group into two groups in order to rule out any medication effects on the results, showed detrimental effects of antidepressants on reward processing. However, this resulted in small sample sizes per subgroup. Interpretation of these results should therefore be done with caution until they can be replicated in larger samples.

Conclusion

The present study showed that MDD is characterized rather by alterations in reward circuit connectivity than isolated activation impairments in brain areas underlying the reward-system. These findings represent an important extension of the existing literature as improved understanding of neural pathways underlying depression-related reward dysfunctions, may help currently unmet diagnostic and therapeutic efforts. The finding that antidepressants might decrease connectivity in the reward-system requires future research with primary interest in the effects of antidepressants in larger samples.

Conflicts of Interest

HGR received speaking fees and an investigator initiated trial (IIT) grant for a different study from Lundbeck.

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Hanneke Geugies
Roel J.T. Mocking
Caroline A. Figueroa
Paul F.C. Groot
Jan-Bernard C. Marsman
Michelle N. Servaas
J. Douglas Steele
Aart H. Schene
Henricus G. Ruhé

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